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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,466	09/10/2004	Marc Ostermeier	56908(71699)	1259

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EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,466	OSTERMEIER, MARC	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,8,14 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,14 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-15-10 has been entered.

Applicant's amendment filed 5-8-09 and 3-15-10 have been entered. Claim 45 has been amended. Claims 1-5, 7, 8, 14 and 45-47 are pending and under consideration.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Lacatena et al., 1994 (PNAS, Vol. 91, pp. 10521-10525).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule

comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Lacatena teaches using TnphoA, a transposon probe for protein export signals, to generate hubeta2AR-phoA fusion protein in vivo by transposition of TnphoA into the hubeta2AR gene in PUC18. Lacatena examined 23 independent Pho+ hubeta2AR:TnphoA insertions and found 13 different fusion sites in the hubeta2AR molecule. The 13 fusion sites are clustered in the first three transmembrane domains and in the C terminus of the hubeta2AR molecule (e.g. bridging p. 10522-10523). PhoA acquires enzymatic activity only when it is translocated to the periplasm, where its intrachain disulfide bonds can form; high activity is observed when the phosphatase domain is located on the outside of the cell membrane, whereas fusions in which phosphatase sequences are located on the inside of the membrane yield low activity (e.g. p. 10523, left column, 2nd full paragraph). "Levels of PhoA activities of fusions with joints located between the N-terminal region and the second hydrophobic domain do not agree with the expected topology of hubeta2AR" (e.g. p. 10524, right column, last paragraph,

Figure 7). Generation of the hubeta2AR-phoA fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. PhoA can be considered as an insertion sequence and the hubeta2AR (human beta2-adrenergic receptor) protein can be considered as an acceptor sequence, which has a deletion, and the insertion is random. Lacatena also teaches fusing the coding region of the hubeta2AR gene to the IPTG-inducible lac promoter (e.g. p. 10522, right column). The IPTG-inducible lac promoter is responsive to IPTG. When IPTG is present, the fusion molecule (lac promoter-hubeta2AR gene) switches state in response to the signal (IPTG). Thus, claims 1-8 and 14 are anticipated by Lacatena.

Applicant argues that the Lacatena reference is a topological analysis of the human beta2 adrenergic receptor in E. coli using hubeta2AR-PhoA fusions and the PhoA activity is used to determine if the hubeta2 AR-PhoA has the correct topology. The fusion taught by Lacatena retains the function of the inserted protein. The claimed invention requires that the state of the polypeptide encoded by the acceptor nucleic acid is coupled to the state of the polypeptide encoded by the insertion nucleic acid or the state of the polypeptide encoded by the insertion nucleic acid is coupled to the state of the polypeptide encoded by the acceptor nucleic acid. The term "coupled" refers to a state which is dependent on another state such that a measurable change in the other state is observed". Applicant argues that Lacatena reference does not teach assembling a modulatable molecule, comprising inserting randomly an insertion sequence into an acceptor sequence and each sequence encodes a polypeptide that comprises a state (amendment, p. 6-12). This is not found persuasive because of the reasons set forth above and the following reasons. Lacatena teaches random insertion of PhoA (alkaline phosphatase) into hubeta2AR

protein by using bacteriophage lamda:TnphoA having a transposon. The transposon can randomly insert into target DNA sequence. Figure 2 of the reference shows various insertion sites of PhoA into hubeta2AR protein from N-terminus to C-terminus. Generation of the hubeta2AR-phoA fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. PhoA can be considered as an insertion sequence and has its state, and the hubeta2AR (human beta2-adrenergic receptor) protein can be considered as an acceptor sequence and has its state. The fusion protein has its own state, and the state of the PhoA is dependent on the state of the hubeta2AR and vice versa. The state of PhoA depends on where it is fused to hubeta2AR and the state of hubeta2AR also depends on how PhoA is fused to hubeta2AR. High activity of PhoA is observed when the phosphatase domain is located on the outside of the cell membrane, whereas fusions in which phosphatase sequences are located on the inside of the membrane yield low activity. "Levels of PhoA activities of fusions with joints located between the N-terminal region and the second hydrophobic domain do not agree with the expected topology of hubeta2AR" (e.g. p. 10524, right column, last paragraph, Figure 7). The IPTG-inducible lac promoter is responsive to IPTG. When IPTG is present, the fusion molecule (lac promoter-hubeta2AR gene) switches state in response to the signal (IPTG). Therefore, Lacatena teaches assembling a modulatable molecule. Thus, the claims are anticipated by Lacatena.

4. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., 2003 (US Patent No. 6,596,485 B2).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Anderson teaches generating random peptide by chemically synthesizing nucleic acid encoding the random peptide, and the nucleic acid and peptide consists of essentially random nucleotides and amino acids (e.g. column 5, lines 13-28). Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position but preferred positions include insertion at the very tips of loops on the surface of the GFP (e.g. column 17, lines 1-38), and "one or more amino acids of the GFP can be deleted and replaced with the peptide" (e.g. column 17, lines 8-10). The derivative GFP contains at least one

amino acid substitution, deletion or insertion that can occur at any residue within the GFP protein (e.g. column 3, lines 28-34). The fusion of GFP with random peptide is used to increase the conformational stability relative to linear peptides or to increase the steady state concentrations of the random peptides (e.g. abstract). The fusion partner of GFP can be a rescue sequence to purify or isolate peptides or a stability sequence to confer stability to the peptide (e.g. column 15, lines 20-22, 35-37). Anderson also teaches the fusion nucleic acids encoding the fusion polypeptide, and expression vector comprising a transcriptional regulatory sequence operably linked to the nucleic acid encoding the fusion protein, wherein the transcriptional regulatory sequence can be a promoter, such as an inducible promoter, for example Tet regulatory element (e.g. column 18, lines 32-55, column 19, lines 19-27). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The peptide can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The inducible promoter, such as Tet regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline). Thus, claims 1-5, 7, 8 and 14 are anticipated by Anderson.

Applicant argues that the GFP and the second or third nucleic acids taught by Anderson do not each comprise a state such that the state of one is coupled to the state of another such that a measurable change in the other state is observed. Anderson teaches to minimize the disruption to the stability of the GFP structure. Anderson does not teach assembling a modulatable

molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the state of the polypeptide encoded by the acceptor nucleic acid is coupled to the state of the polypeptide encoded by the insertion nucleic acid or the state of the polypeptide encoded by the insertion nucleic acid is coupled to the state of the polypeptide encoded by the acceptor nucleic acid (amendment, p. 12-13). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102(e) rejection. Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position. The random peptide, GFP, rescue sequence or stability sequence each has its own state, and the generated fusion protein has its own state. The fusion of GFP with random peptide is used to increase the conformational stability relative to linear peptides or to increase the steady state concentrations of the random peptides. It is apparent that the state of random peptides is dependent on the state of GFP and the state of random peptides is "coupled" to the stat of the GFP. Further, the inducible promoter, such as Tet regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline). Therefore, the Anderson teaches assembling a modulatable molecule. Thus, the claims are anticipated by Anderson.

5. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Manoil et al., 1990 (Journal of Bacteriology, Vol. 172, No. 2, p. 515-518).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Manoil teaches using a transposon derivative of Tn5 (TnphoA) containing a phoA gene missing its promoter, its translation initiation site, and DNA corresponding to the signal sequence and first five amino acids of the protein, to insert into a gene to generate hybrid proteins. The insertion of TnphoA into a gene (transposon insertion) is random and the fusion gene encoding hybrid proteins with alkaline phosphatase activity are detected as blue colonies on media containing the alkaline phosphatase indicator dye (e.g. p. 515, right column). Manoil reports that "The basis of the alkaline phosphatase fusion approach is the finding that the activity of the enzyme responds differently to different environments" (e.g. p. 517, right column).

Generation of the hybrid proteins constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The resulting hybrid protein or gene encoding said hybrid protein is a new state. PhoA gene can be considered as an insertion sequence and the target gene can be considered as an acceptor sequence, and the insertion is random. Thus, the claims are anticipated by Manoil.

Applicant argues that Manoil does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 13-14). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102(b) rejection. Each of the PhoA and the polypeptide encoded by the inserted gene has its state and the generated hybrid protein has its state. Since the activity of the enzyme in alkaline phosphatase hybrid protein responds differently to different environments, the generated hybrid protein is a modulatable molecule. Thus, the claims are anticipated by Manoil.

6. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Mountford et al., 1995 (TIG, Vol. 11, No. 5, p. 179-184).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in

response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7 and 8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state.

Mountford teaches gene trapping for identifying developmentally regulated genes based on the random integration of a reporter into chromosomal transcription units. Mountford further teaches that IRES-containing gene trap construct pGT1.8Iresbetageo enhances frequency of productive integration as compared to control vector (e.g. p. 182, right column). The gene trap vector is an insertion sequence and the choromosomal transcription units are acceptor sequences. The resulting fusion molecule is a new state. A fusion protein can respond to a stimulator or inhibitor, therefore, the fusion protein is a modulatable molecule. Thus, the claims are anticipated by Mountford.

Applicant argues that Mountford does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 14-15). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102(b) rejection.

7. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Ong, Christopher, 2005 (US Patent No. 6,867,035 B2).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Ong teaches preparation of gene trap DNA construct comprising a mutagenic, detectable component containing a IRES linked to a reporter gene and a functional unit comprising a reporter gene under the control of PGK promoter. Transfection of the gene trap construct via electroporation into ES cells results in random integration into ES cell genome by illegitimate recombination. The trap vector not only introduces a molecular tag that permits subsequent cloning and identification, chromosomal localization and placement onto the physical map of the

trapped gene, but also generates ES cells bearing mutations in the respective gene (e.g. column 7, lines 8-47). The gene trap DNA construct is an insertion sequence and the ES cell genome is acceptor sequence. The resulting fusion molecule is a new state. A fusion protein can respond to a stimulator or inhibitor, therefore, the fusion protein is a modulatable molecule. Thus, the claims are anticipated by Ong.

Applicant argues that Ong does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 15). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102(e) rejection.

8. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Heintz et al., 2002 (US Patent No. 6,485,912 B1).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a

fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Heintz teaches gene trapping in bacterial artificial chromosomes (BACs) by using randomized gene trapping having promoter-5' exon element randomly inserted into a BAC via a Tn 10 transposon system. Randomized gene trapping involves the relatively random insertion of a PEU into a BAC mediated transposon system, such as Tn10 or Tn3 (e.g. detailed description text (77), (83)). The gene trap vector is an insertion sequence and the BAC is an acceptor sequence. The resulting fusion molecule is a new state. Thus, the claims are anticipated by Heintz.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., 2003 (US Patent No. 6,596,485 B2) in view of Norris, 2006 (US Patent No. 7,135,176).

Claims 1 and 45-47 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state, wherein the inserting randomly comprises one or more of a method selected from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment, or further comprises generating a duplication, deletion, substitution at the insertion site in the acceptor sequence. Claim 47 specifies the nuclease treatment comprises digestion with a 3' to 5' exonuclease.

Anderson teaches generating random peptide by chemically synthesizing nucleic acid encoding the random peptide, and the nucleic acid and peptide consists of essentially random nucleotides and amino acids (e.g. column 5, lines 13-28). Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position but preferred positions include insertion at the very tips of loops on the surface of the GFP (e.g. column 17, lines 1-38), and "one or more amino acids of the GFP can be deleted and replaced with the peptide" (e.g. column 17, lines 8-10). The derivative GFP contains at least one amino acid substitution, deletion or insertion that can occur at any residue within the GFP protein (e.g. column 3, lines 28-34). Anderson also teaches the fusion nucleic acids encoding the fusion polypeptide, and expression vector comprising a transcriptional regulatory sequence operably linked to the nucleic acid encoding the fusion protein, wherein the transcriptional regulatory sequence can be a promoter, such as an inducible promoter, for example Tet regulatory element

(e.g. column 18, lines 32-55, column 19, lines 19-27). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The peptide can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The inducible promoter, such as Tet regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline).

Anderson does not specifically teach DNase treatment or 3' to 5' exonuclease treatment.

Norris teaches random cloning of lamda.DASH-Bb12 insert by treating purified bacteriophage DNA with DNase I in the presence of Mn2+ and cloned into EcoRV-digested pBluescript II SK(-) (description paragraph (161)).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use DNase I to treat a DNA for random cloning because Anderson teaches generating random peptide by chemically synthesizing nucleic acid encoding the random peptide, and insertion of the nucleic acid to nucleic acid encoding GFP, and Norris teaches using DNase I to produce random nucleic acid for random cloning of said nucleic acid into a vector. Both Anderson and Norris teaches producing random nucleic acid sequences with different lengths for cloning. It also would have been obvious for one of ordinary skill in the art to use 3' to 5' exonuclease to generate different lengths of nucleic acid sequences because it was known in the art that 3' to 5' exonuclease can digest nucleic acid sequence to diverse extent to create different lengths of nucleic acid sequences.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order for random cloning of nucleic acid into a vector as taught by Norris or into a target sequence, such as GFP, as taught by Anderson with reasonable expectation of success.

Applicant argues that Anderson and Norris fail to teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, wherein the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 15). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 102(e) and 103(a) rejections.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.
/Shin-Lin Chen/
Primary Examiner, Art Unit 1632